GREENE'S PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

Fourth Edition

PETER G. M. WUTS

Pfizer

and

THEODORA W. GREENE

The Rowland Institute for Science



WILEY-INTERSCIENCE
A John Wiley & Sons, Inc., Publication

GREENE'S PROTECTIVE GROUPS IN ORGANIC SYNTHESIS



THE WILEY BICENTENNIAL-KNOWLEDGE FOR GENERATIONS

ach generation has its unique needs and aspirations. When Charles Wiley first opened his small printing shop in lower Manhattan in 1807, it was a generation of boundless potential searching for an identity. And we were there, helping to define a new American literary tradition. Over half a century later, in the midst of the Second Industrial Revolution, it was a generation focused on building the future. Once again, we were there, supplying the critical scientific, technical, and engineering knowledge that helped frame the world. Throughout the 20th Century, and into the new millennium, nations began to reach out beyond their own borders and a new international community was born. Wiley was there, expanding its operations around the world to enable a global exchange of ideas, opinions, and know-how.

For 200 years, Wiley has been an integral part of each generation's journey, enabling the flow of information and understanding necessary to meet their needs and fulfill their aspirations. Today, bold new technologies are changing the way we live and learn. Wiley will be there, providing you the must-have knowledge you need to imagine new worlds, new possibilities, and new opportunities.

Generations come and go, but you can always count on Wiley to provide you the knowledge you need, when and where you need it!

WILLIAM **J. P**ESCE

PRESIDENT AND CHIEF EXECUTIVE OFFICER

PETER BOOTH WILEY CHAIRMAN OF THE BOARD

GREENE'S PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

Fourth Edition

PETER G. M. WUTS

Pfizer

and

THEODORA W. GREENE

The Rowland Institute for Science



WILEY-INTERSCIENCE
A John Wiley & Sons, Inc., Publication

Copyright © 2007 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at http://www.wiley.com/go/permission.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Wuts, Peter G. M.

Greene's protective groups in organic synthesis. – 4th ed. / Peter G. M. Wuts,

Theodora W. Greene

p. cm.

Greene's name appears first on the earlier edition.

Includes index.

ISBN-13: 978-0-471-69754-1 (cloth)

ISBN-10: 0-471-69754-0 (cloth)

1. Organic compounds—Synthesis. 2. Protective groups (Chemistry) I. Greene, Theodora W., 1931-Protective groups in organic synthesis. II. Title.

QD262.G665 2006

547.2-dc22 2006016601

Printed in the United States of America

CONTENTS

Pr	eface to the Fourth Edition	ix
Pr	eface to the Third Edition	xi
Pr	eface to the Second Edition	xiii
Pr	eface to the First Edition	XV
Ab	breviations	xvii
1.	The Role of Protective Groups in Organic Synthesis	1
2.	Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols	16
	Ethers, 24	
	Esters, 222	
	Protection for 1,2- and 1,3-Diols, 299	
3.	Protection for Phenols and Catechols	367
	Protection for Phenols, 370	
	Ethers, 370	
	Silyl Ethers, 406	
	Esters, 410	
	Carbonates, 416	
	Aryl Carbamates, 419	
	Phosphinates, 420	
	Sulfonates, 421	

vi CONTENTS

	Protection for Catechols, 424 Cyclic Acetals and Ketals, 424 Cyclic Esters, 428	
	Protection for 2-Hydroxybenzenethiols, 430	
4.	Protection for the Carbonyl Group	431
	Acetals and Ketals, 435 Miscellaneous Derivatives, 506 Monoprotection of Dicarbonyl Compounds, 528	
5.	Protection for the Carboxyl Group	533
	Esters, 538 Amides and Hydrazides, 632 Protection of Boronic Acids, 643 Protection of Sulfonic Acids, 645	
6.	Protection for the Thiol Group	647
	Thioethers, 650 Thioesters, 682 Miscellaneous Derivatives, 687	
7.	Protection for the Amino Group	696
	Carbamates, 706 Amides, 773 Special—NH Protective Groups, 803 Protection for Imidazoles, Pyrroles, Indoles, and other Aromatic Heterocycles, 872 Protection for the Amide —NH, 894 Protection for the Sulfonamide —NH, 916	
8.	Protection for the Alkyne –CH	927
9.	Protection for the Phosphate Group	934
	Some General Methods for Phosphate Ester Formation, 939 Removal of Protective Groups from Phosphorus, 940 Alkyl Phosphates, 944 Phosphates Cleaved by Cyclodeesterification, 952 Benzyl Phosphates, 966 Phenyl Phosphates, 972 Photochemically Cleaved Phosphate Protective Groups, 980 Amidates, 983 Miscellaneous Derivatives, 985	

CONTENTS vii

10. Reactivities, Reagents, and Reactivity Charts	986
---	-----

Reactivities, 986

Reagents, 987

Reactivity Charts, 990

- 1 Protection for the Hydroxyl Group: Ethers, 992
- 2 Protection for the Hydroxyl Group: Esters, 997
- 3 Protection for 1,2- and 1,3-Diols, 1001
- 4 Protection for Phenols and Catechols, 1005
- 5 Protection for the Carbonyl Group, 1009
- 6 Protection for the Carboxyl Group, 1013
- 7 Protection for the Thiol Group, 1017
- 8 Protection for the Amino Group: Carbamates, 1021
- 9 Protection for the Amino Group: Amides, 1025
- 10 Protection for the Amino Group: Special -NH Protective Groups, 1029
- 11 Selective Deprotection of Silyl Ethers, 1033

Index 1053

PREFACE TO THE FOURTH EDITION

After completing the mammoth third edition, I never imagined that a fourth edition would eventuate because of the sheer volume of literature that must be examined to cover the subject comprehensively. Nonetheless, I took on the task with the encouragement and help of my wife, Lizzie, who agreed to assist me with this one, since Theo was not able to. As with the last edition, the searches were primarily done by hand because databases such as Scifinder fail to be selective and have such a prodigious output that no one can be expected to filter all that material in a reasonable amount of time. Nevertheless, Scifinder was used to locate material in journals which were not readily accessible. In recent years, in both corporate and academic America, there has also been a trend to do away with physical libraries, which makes doing a literature search extremely difficult, especially if you like reading the literature at home in a comfortable chair. Reading journals on a computer screen may be easy for Spock, but I find it difficult and stressful. With limited access to hard copies of some of the literature, I may have missed some things. For this I apologize and will not be offended if the author sends me the material for inclusion in a possible future edition. The literature search is complete through the end of 2005.

With that said, the fourth edition contains over 3100 new references compared to the 2349 new citations in the third edition. In keeping with the tradition of the past, I tried to include material covering new methods for existing protective groups along with new groups that have been developed. When the authors disclosed the information, I also provided the rationale for the choice of a given protective group. In that synthetic chemistry is still not sufficiently developed to do away with protective groups altogether, I have included many examples that highlight selective protection and deprotection, especially when the selectivity might not be totally obvious or expected. Issues of unexpected reactivity are also included, since these cases should

help in choosing a group during the development of a synthetic plan. On the whole, this is a book of options for the synthetic chemist, since no one method is suitable for all occasions. Also, many of the published methods have not been tested in complex situations; thus it is impossible to determine which method of a particular set might be the best, and, as such, no attempt was made to try and order the various methods that appear in a section. The issue of functional group compatibility is often not addressed in papers describing new methods, and this further complicates the evaluation process. Comparative studies for either protection or deprotection are rarely done and as a result, trial and error and chemical intuition must be used to define the most suitable method in a given situation.

All sections of the book have seen some expansion, especially the chapters on alcohol and amine protection. I had considered adding a section that covered areas such as diene protection as metal complexes and Diels—Alder adducts, but the use of these is rather limited. The Reactivity Charts of Chapter 10 have not been altered, but a new chart covering selectivity in silyl group deprotection has been added. The overall format of the book has been retained and in some of the larger sections, similar methods have been grouped together. A new area has emerged since the last edition, and this is the use of fluorous protective groups. These have been included and placed in the appropriate sections rather than having collected them together.

The completion of this project was aided by a number of people. First of all this work would not have been started without the encouragement and dedication of my wife, Lizzie, who looked up and downloaded many of the references and then typed every new reference into an EndnoteTM database. She double-checked the entire set in order to prevent errors. She also read through the entire manuscript to check it for punctuation, grammar, and consistency. She has a degree in Near Eastern Medieval History, thus I take full responsibility for any chemical errors. I must also thank her for not complaining about becoming a book widow while I spent countless hours on this project over a period of ~3 years. A special note of thanks must be extended to Peter Green, the Pfizer Michigan site head, who approved giving Lizzie access to the company library system even though she was not an employee. I would also like to thank Jake Szmuszkovicz, Raymond Conrow, and Martin Lang for providing me with references to be included in the fourth edition, and finally I wish to thank Joseph Muchowski for bringing an error in the third edition, now corrected, to my attention.

PETER G. M. WUTS

PREFACE TO THE THIRD EDITION

Organic synthesis has not yet matured to the point where protective groups are not needed for the synthesis of natural and unnatural products; thus, the development of new methods for functional group protection and deprotection continues. The new methods added to this edition come from both electronic searches and a manual examination of all the primary journals through the end of 1997. We have found that electronic searches of *Chemical Abstracts* fail to find many new methods that are developed during the course of a synthesis, and issues of selectivity are often not addressed. As with the second edition, we have attempted to highlight unusual and potentially useful examples of selectivity for both protection and deprotection. In some areas the methods listed may seem rather redundant, such as the numerous methods for THP protection and deprotection, but we have included them in an effort to be exhaustive in coverage. For comparison, the first edition of this book contains about 1500 references and 500 protective groups, the second edition introduces an additional 1500 references and 206 new protective groups, and the third edition adds 2349 new citations and 348 new protective groups.

Two new sections on the protection of phosphates and the alkyne-CH are included. All other sections of the book have been expanded, some more than others. The section on the protection of alcohols has increased substantially, reflecting the trend of the nineties to synthesize acetate- and propionate-derived natural products. An effort was made to include many more enzymatic methods of protection and deprotection. Most of these are associated with the protection of alcohols as esters and the protection of carboxylic acids. Here we have not attempted to be exhaustive, but hopefully, a sufficient number of cases are provided that illustrate the true power of this technology, so that the reader will examine some of the excellent monographs and review articles cited in the references. The Reactivity Charts in Chapter 10 are

identical to those in the first edition. The chart number appears beside the name of each protective group when it is first introduced. No attempt was made to update these Charts, not only because of the sheer magnitude of the task, but because it is nearly impossible in a two-dimensional table to address adequately the effect that electronic and steric controlling elements have on a particular instance of protection or deprotection. The concept of fuzzy sets as outlined by Lofti Zadeh would be ideally suited for such a task.

The completion of this project was aided by the contributions of a number of people. I am grateful to Rein Virkhaus and Gary Callen, who for many years forwarded me references when they found them, to Jed Fisher for the information he contributed on phosphate protection, and to Todd Nelson for providing me a preprint of his excellent review article on the deprotection of silyl ethers. I heartily thank Theo Greene for checking and rechecking the manuscript—all 15 cm of it—for spelling and consistency and for the arduous task of checking all the references for accuracy. I thank Fred Greene for reading the manuscript, for his contribution to Chapter 1 on the use of protective groups in the synthesis of himastatin, and for his contribution to the introduction to Chapter 9, on phosphates. I thank my wife, Lizzie, for encouraging me to undertake the third edition, for the hours she spent in the library looking up and photocopying hundreds of references, and for her understanding while I sat in front of the computer night after night and numerous weekends over a two-year period. She is the greatest!

PETER G. M. WUTS

Kalamazoo, Michigan June 1998

PREFACE TO THE SECOND EDITION

Since publication of the first edition of this book in 1981, many new protective groups and many new methods of introduction or removal of known protective groups have been developed: 206 new groups and approximately 1500 new references have been added. Most of the information from the first edition has been retained. To conserve space, generic structures used to describe Formation/Cleavage reactions have been replaced by a single line of conditions, sometimes with explanatory comments, especially about selectivity. Some of the new information has been obtained from on-line searches of *Chemical Abstracts*, which have limitations. For example, *Chemical Abstracts* indexes a review article about protective groups only if that word appears in the title of the article. References are complete through 1989. Some references, from more widely circulating journals, are included for 1990.

Two new sections on the protection for indoles, imidazoles, and pyrroles and protection for the amide –NH are included. They are separated from the regular amines because their chemical properties are sufficiently different to affect the chemistry of protection and deprotection. The Reactivity Charts in Chapter 8 are identical to those in the first edition. The chart number appears beside the name of each protective group when it is first discussed.

A number of people must be thanked for their contributions and help in completing this project. I am grateful to Gordon Bundy, who loaned me his card file, which provided many references that the computer failed to find, and to Bob Williams, Spencer Knapp, and Tohru Fukuyama for many references on amine and amide protection. I thank Theo Greene who checked and rechecked the manuscript for spelling and consistency and for the herculean task of checking all the references to make sure that my 3's and 8's and 7's and 9's were not interchanged—all done without a single complaint. I thank Fred Greene who read the manuscript and provided

valuable suggestions for its improvement. My wife Lizzie was a major contributor to getting this project finished, by looking up and photocopying references, by turning on the computer in an evening ritual, and by typing many sections of the original book, which made the changes and additions much easier. Without her understanding and encouragement, the volume probably would never have been completed.

PETER G. M. WUTS

Kalamazoo, Michigan May 1990

PREFACE TO THE FIRST EDITION

The selection of a protective group is an important step in synthetic methodology, and reports of new protective groups appear regularly. This book presents information on the synthetically useful protective groups (~500) for five major functional groups: -OH, -NH, -SH, -COOH, and >C=O. References through 1979, the best method(s) of formation and cleavage, and some information on the scope and limitations of each protective group are given. The protective groups that are used most frequently and that should be considered first are listed in Reactivity Charts, which give an indication of the reactivity of a protected functionality to 108 prototype reagents.

The first chapter discusses some aspects of protective group chemistry: the properties of a protective group, the development of new protective groups, how to select a protective group from those described in this book, and an illustrative example of the use of protective groups in a synthesis of brefeldin. The book is organized by functional group to be protected. At the beginning of each chapter are listed the possible protective groups. Within each chapter protective groups are arranged in order of increasing complexity of structure (e.g., methyl, ethyl, *t*-butyl,..., benzyl). The most efficient methods of formation or cleavage are described first. Emphasis has been placed on providing recent references, since the original method may have been improved. Consequently, the original reference may not be cited; my apologies to those whose contributions are not acknowledged. Chapter 8 explains the relationship between reactivities, reagents, and the Reactivity Charts that have been prepared for each class of protective groups.

This work has been carried out in association with Professor Elias J. Corey, who suggested the study of protective groups for use in computer-assisted synthetic analysis. I appreciate his continued help and encouragement. I am grateful to Dr. J. F. W.

McOmie (Ed., *Protective Groups in Organic Chemistry*, Plenum Press, New York and London, 1973) for his interest in the project and for several exchanges of correspondence, and to Mrs. Mary Fieser, Professor Frederick D. Greene, and Professor James A. Moore for reading the manuscript. Special thanks are also due to Halina and Piotr Starewicz for drawing the structures, and to Kim Chen, Ruth Emery, Janice Smith, and Ann Wicker for typing the manuscript.

THEODORA W. GREENE

Harvard University September 1980

ABBREVIATIONS

PROTECTIVE GROUPS

In some cases, several abbreviations are used for the same protective group. We have listed the abbreviations as used by an author in his original paper, including capital and lowercase letters. Occasionally, the same abbreviation has been used for two different protective groups. This information is also included.

ABO 2,7,8-trioxabicyclo[3.2.1]octyl

Ac acetyl

ACBZ 4-azidobenzyloxycarbonyl
ACE O-bis(2-Acetoxyethoxy)methyl
AcHmb 2-acetoxy-4-methoxybenzyl

Acm acetamidomethyl Ad 1-adamantyl

ADMB 4-acetoxy-2,2-dimethylbutanoate

Adoc 1-adamantyloxycarbonyl

Adpoc 1-(1-adamantyl)-1-methylethoxycarbonyl

Alloc or AOC allyloxycarbonyl AOC or Alloc allyloxycarbonyl

Allocam allyloxycarbonylaminomethyl

Als allylsulfonyl

AMB 2-(acetoxymethyl)benzoyl AMPA (2-azidomethyl)phenylacetate AN 4-methoxyphenyl or anisyl

Ans anisylsulfonyl

xviii ABBREVIATIONS

Anpe 2-(4-acetyl-2-nitrophenyl)ethyl

p-AOM *p*-anisyloxymethyl or (4-methoxyphenoxy)methyl

APAC 2-allyloxyphenylacetate

Aqmoc anthraquinone-2-ylmethoxycarbonyl

Azb p-azidobenzyl Azm azidomethyl

AZMB 2-(azidomethyl)benzoate
Bam benzamidomethyl
BBA butane-2,3-bisacetal
Bbc but-2-ynylbisoxycaronyl
BDIPS biphenyldiisopropylsilyl
BDMS biphenyldimethylsilyl

benzyldimethylsilyl

Bdt 1,3-benzodithiolan-2-yl Betsyl or Bts benzothiazole-2-sulfonyl

Bhcmoc 6-bromo-7-hydroxycoumarin-4-ylmethoxycarbonyl

BHQ 8-bromo-7-hydroxyquinoline-2-ylmethyl

BHT 2,6-di-*t*-butyl-4-methylphenyl
Bic 5-benzisoxazolylmethoxycarbonyl

Bim 5-benzisoazolylmethylene

Bimoc benz[f]inden-3-ylmethoxycarbonyl
BIPSOP N-2,5-bis(triisopropylsiloxy)pyrrolyl
BMB o-(benzoyloxymethyl)benzoyl
Bmpc 2,4-dimethylthiophenoxycarbonyl
Bmpm bis(4-methoxyphenyl)-1'-pyrenylmethyl

Bn benzyl

Bnf fluorousbenzyl

Bnpeoc 2,2-bis(4'-nitrophenyl)ethoxycarbonyl

BOB benzylsulfonate benzyloxybutyrate BOC t-butoxycarbonyl

Bocdene 2-(*t*-butylcarbonyl)ethylidene

BOM benzyloxymethyl

Bpoc 1-methyl-1-(4-biphenyl)ethoxycarbonyl

BSB benzoSTABASE

Bsmoc 1,1-dioxobenzo[*b*]thiophene-2-ylmethoxycarbonyl

BTM *t*-butylthiomethyl

Bts or Betsyl benzothiazole-2-sulfonyl B^tSE 2-t-butylsulfonylethyl

Bts-Fmoc 2,7-bis(trimethylsilyl)fluorenylmethoxycarbonyl

Bum *t*-butoxymethyl
Bus *t*-butylsulfonyl

t-Bumeoc 1-(3,5-di-*t*-butylphenyl)-1-methylethoxycarbonyl

Bz benzoyl

CAEB 2-[(2-chloroacetoxy)ethyl]benzoyl

PROTECTIVE GROUPS xix

Cam carboxamidomethyl

CAMB 2-(chloroacetoxymethyl)benzoyl

benzyloxycarbonyl Cbz or Z CEM 2-cyanoethoxymethyl cyclohexane-1,2-diacetal CDA **CDM** 2-cyano-1,1-dimethylethyl

CE or Cne 2-cyanoethyl

Cee 1-(2-chloroethoxy)ethyl CEE 1-(2-cyanoethoxy)ethyl cyclic ethyl orthoformate Ceof

cvclohexvl cHex Chx cyclohexyl Cin cinnamyl

ClAzab 4-azido-3-chlorobenzyl

Climoc 2-chloro-3-indenylmethoxycarbonyl

carboxymethylsulfenyl Cms **CNAP** 2-naphthylmethoxycarbonyl

Cne or CE 2-cyanoethyl

Coc cinnamyloxycarbonyl CPC p-chlorophenylcarbonyl (3-cyanopropyl)dimethylsilyl **CPDMS** 2-(cyano-1-phenyl)ethoxycarbonyl Cpeoc

Cpep 1-(4-chlorophenyl)-4-methoxypiperidin-4-yl CPTr 4,4',4"-tris(4,5-dichlorophthalimido)-

triphenylmethyl

CTFB 4-trifluoromethylbenzyloxycarbonyl 1-[(2-chloro-4-methyl)phenyl]-4-**CTMP**

methoxypiperidin-4-yl

5-trimethylsilyl-1,3-dioxane Cyclo-SEM

Cys cysteine

DAM di-p-anisylmethyl or bis(4-methoxyphenyl)methyl

1,1-di-p-anisyl-2,2,2-trichloroethyl DATE 1,1-dimethyl-2,2-dibromoethoxycarbonyl DB-t-BOC DBD-Tmoc 2,7-di-t-butyl[9-(10,10-dioxo-10,10,10,10-tetra=

hydrothioxanthyl)]methoxycarbonyl

DBS dibenzosuberyl DCP dichlorophthalimide Dcpm dicyclopropylmethyl

bis(4-methoxyphenyl)methyl Ddm or Dmbh

2-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl Dde 1-methyl-1-(3,5-dimethoxyphenyl)ethoxycarbonyl Ddz

DEM diethoxymethyl **DEIPS** diethylisopropylsilyl Desvl 2-oxo-1,2-diphenylethyl 1,3-dithianyl-2-methyl Dim

xx ABBREVIATIONS

Dmab 4-{*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-

3-methylbutyl]amino}benzyl

DMB "3',5'-dimethoxybenzoin"
Dmb 2,4-dimethoxybenzyl

DMBM [(3,4-dimethoxybenzyl)oxy]methyl

DMIPS dimethylisopropylsilyl
DMN 2,3-dimethylmaleimide
Dmoc dithianylmethoxycarbonyl
Dmp 2,4-dimethyl-3-pentyl
Dmp dimethylphosphinyl
DMP dimethoxyphenyl

dimethylphenacyl

DMPM 3,4-dimethoxybenzyl DMTC dimethylthiocarbamate

 $\begin{array}{ll} {\rm DMT\ or\ DMT} & {\rm di}(p\mbox{-methoxyphenyl}) \mbox{phenylmethyl\ or\ dimethoxytrityl} \\ {\rm DMTr\ or\ DMT} & {\rm di}(p\mbox{-methoxyphenyl}) \mbox{phenylmethyl\ or\ dimethoxytrityl} \end{array}$

DNAP 2-(dimethylamino)-5-nitrophenyl

DNB p,p'-dinitrobenzhydryl

DNMBS 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl

DNP 2,4-dinitrophenyl

Dnpe 2-(2,4-dinitrophenyl)ethyl

Dnpeoc 2-(2,4-dinitrophenyl)ethoxycarbonyl

DNs 2,4-dinitrobenzenesulfonyl

DNse 2-(2,4-dinitrophenylsulfonyl)ethoxycarbonyl

Dnseoc 2-dansylethoxycarbonyl

Dobz p-(dihydroxyboryl)benzyloxycarbonyl
Doc 2,4-dimethylpent-3-yloxycarbonyl
Dod bis(4-methoxylphenyl)methyl

DOPS dimethyl[1,1-dimethyl-3-(tetrahydro-2*H*-pyran-2-

yloxy)propyl]silyl

DPA diphenylacetyl
DPIPS diphenylisopropylsilyl
DPM or Dpm diphenylmethyl
DPMS diphenylmethylsilyl
Dpp diphenylphosphinyl

 Dppe
 2-(diphenylphosphino)ethyl

 Dppm
 (diphenyl-4-pyridyl)methyl

 DPSE
 2-(methyldiphenylsilyl)ethyl

 DPSide
 diphenylsilyldiethylene

 Dpt
 diphenylphosphinothioyl

 DPTBOS
 t-Butoxydiphenylsilyl

 DPTBS
 diphenyl-t-butoxysilyl or

diphenyl-t-butylsilyl

Dtb-Fmoc 2,6-di-*t*-butyl-9-fluorenylmethoxycarbonyl

DTBMS di-t-butylmethylsilyl

PROTECTIVE GROUPS xxi

DTBS di-t-butylsilylene

DTE 2-(hydroxyethyl)dithioethyl or "dithiodiethanol"

Dts dithiasuccinimidyl

E-DMT 1,2-ethylene-3,3-bis(4'4"-dimethoxytrityl)

EE 1-ethoxyethyl EOM ethoxymethyl

FCbz fluorous benzyloxycarbonyl

Fcm ferrocenylmethyl

Flu fluorenyl

Fm 9-fluorenylmethyl

Fmoc 9-fluorenylmethoxycarbonyl

Fpmp 1-(2-fluorophenyl)-4-methoxypiperidiny-4-yl

GUM guaiacolmethyl

HAPE 1-[2-(2-hydroxyalkyl)phenyl]ethanone

HBn 2-hydroxybenzyl Hdoc hexadienyloxycarbonyl HFB hexafluoro-2-butyl

HIP 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl

Hoc cyclohexyloxycarbonyl

HSDIS (hydroxystyryl)diisopropylsilyl HSDMS (hydroxystyryl)dimethylsilyl hZ or homo Z homobenzyloxycarbonyl IDTr 3-(imidazol-1-ylmethyl)-4',4"-

dimethoxytriphenylmethyl

IETr 4,4'-dimethoxy-3"-[N-(imidazolylethyl)

carbamoyl]trityl

iMds 2,6-dimethoxy-4-methylbenzenesulfonyl

Ipaoc 1-isopropylallyloxycarbonyl

Ipc isopinocampheyl IPDMS isopropyldimethylsilyl

Lev levulinoyl

LevS 4,4-(ethylenedithio)pentanoyl LevS levulinoyldithioacetal ester

LMMo(p)NBz 6-(levulinyloxymethyl)-3-methoxy-2-nitrobenzoate

MAB 2-{{[(4-methoxytrityl)thio]methylamino}

methyl}benzoate

MAQ 2-(9,10-anthraquinonyl)methyl or

2-methyleneanthraquinone

MBE 1-methyl-1-benzyloxyethyl Mbh bis(4-methylphenyl)methyl

MBF 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-

methanobenzofuran-2-yl

MBS or Mbs p-methoxybenzenesulfonyl MCPM 1-methyl-1'-cyclopropylmethyl

Mds 2,6-dimethyl-4-methoxybenzenesulfonyl

xxii ABBREVIATIONS

MDPS methylene-bis-(diisopropylsilanoxanylidene

Me methyl

MEmethoxyethylMECα-methylcinnamylMeemethoxyethoxyethylMeOAcmethoxyacetate

MEM 2-methoxyethoxymethyl

Menpocα-methylnitropiperonyloxycarbonylMeOZ or Mozp-methoxybenzyloxycarbonylMesmesityl or 2,4,6-trimethylphenyl

MIP methoxyisopropyl or 1-methyl-1-methoxyethyl

MM menthoxymethyl

 $\begin{array}{ll} \text{MMT or MMTr} & p\text{-methoxyphenyldiphenylmethyl} \\ \text{MMTr or MMT} & p\text{-methoxyphenyldiphenylmethyl} \end{array}$

MMPPOC 2-(3,4-methylenedioxy-6-

nitrophenypropyloxycarbonyl

MOB 2-{[(4-methoxytritylthio)oxy]methyl}benzoate

Mocdene 2-(methoxycarbonyl)ethylidene

MoEt 2-*N*-(morpholino)ethyl

MOM methoxymethyl moMO methoxymethoxy

Moz or MeOZ p-methoxybenzyloxycarbonyl

MP *p*-methoxyphenyl Mpe 3-methyl-3-pentyl

MPM or PMB p-methoxyphenylmethyl or p-methoxybenzyl

 $\begin{array}{lll} \text{Mps} & p\text{-methoxyphenylsulfonyl} \\ \text{Mpt} & \text{dimethylphosphinothioyl} \\ \text{Ms} & \text{methanesulfonyl or mesyl} \\ \text{MSE} & 2\text{-(methylsulfonyl)ethyl} \\ \text{Msib} & 4\text{-(methylsulfinyl)benzyl} \end{array}$

Mspoc 2-methylsulfonyl-3-phenyl-1-prop-2-enyloxy

Msz 4-methylsulfinylbenzyloxycarbonyl MTAD 4-methyl-1,2,4-triazoline-3,5-dione Mtb 2,4,6-trimethoxybenzenesulfonyl

Mte 2,3,5,6-tetramethyl-4-methoxybenzenesulfonyl

MTHP 4-methoxytetrahydropyranyl

MTM methylthiomethyl

MTMB 4-(methylthiomethoxy)butyryl

MTMECO 2-(methylthiomethoxy)ethoxycarbonyl MTMT 2-(methylthiomethoxymethyl)benzoyl Mtpc 4-(methylthio)phenoxycarbonyl

Mtr 2,3,6-trimethyl-4-methoxybenzenesulfonyl

Mts 2,4,6-trimethylbenzenesulfonyl or mesitylenesulfonyl

Mtt 4-methoxytrityl or 4-methyltrityl

Nap 2-napthylmethyl

PROTECTIVE GROUPS xxiii

NBOM nitrobenzyloxymethyl
NBM nitrobenzyloxymethyl
NDMS 2-norbornyldiemethylsilyl

Ne 2-nitroethyl

Noc 4-nitrocinnamyloxycarbonyl Nosyl or Ns 2- or 4-nitrobenzenesulfonyl

Npe or npe 2-(nitrophenyl)ethyl

Npeoc2-(4-nitrophenyl)ethoxycarbonylNpeom[1-(2-nitrophenyl)ethoxy]methylNpes2-(4-nitrophenyl)ethylsulfonylNPPOC2-(2-nitrophenyl)propyloxycarbonyl

NPS or Nps 2-nitrophenylsulfenyl

NpSSPeoc 2-[(2-nitrophenyl)dithio]-1-phenylethoxycarbonyl

Npys 3-nitro-2-pyridinesulfenyl Ns or Nosyl 2- or 4-nitrobenzenesulfonyl

Nse 2-(4-nitrophenylsulfonyl)ethoxycarbonyl NVOC or Nvoc 3,4-dimethoxy-6-nitrobenzyloxycarbonyl or

6-nitroveratryloxycarbonyl

OBO 2,6,7-trioxabicyclo[2.2.2]octyl O-DMT 3,3'-oxybis(dimethoxytrityl)

ONB o-nitrobenzyl
PAB p-acylaminobenzyl
PAB acetoxybenzyl

PAC_H 2-[2-(benzyloxy)ethyl]benzoyl

PAC_M 2-[2-(4-methoxybenzyloxy)ethyl]benzoyl

Paloc 3-(3-pyridyl)allyloxycarbonyl or

3-(3-pyridyl)prop-2-enyloxycarbonyl

Pbf 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl

PeNB pentadienylnitrobenzyl
PeNP pentadienylnitropiperonyl
Peoc 2-phosphonioethoxycarbonyl

Peoc 2-(triphenylphosphonio)ethoxycarbonyl

Pet 2-(2'-pyridyl)ethyl
Pf 9-phenylfluorenyl
Pfp pentafluoropenyl
Phamc phenylacetamidomethyl

PhAc 4-phenylacetoxybenzyloxycarbonyl Phenoc 4-methoxyphenacyloxycarbonyl

Pic picolinate

Pim phthalimidomethyl Pixyl or Px 9-(9-phenyl)xanthenyl

PMB or MPM *p*-methoxybenzyl or *p*-methoxyphenylmethyl

PMBM *p*-methoxybenzyloxymethyl

Pmc 2,2,5,7,8-pentamethylchroman-6-sulfonyl

Pme pentamethylbenzenesulfonyl

xxiv ABBREVIATIONS

PMP *p*-methoxyphenyl PMS *p*-methylbenzylsulfonyl

Pms 2-[phenyl(methyl)sulfonio]ethoxycarbonyl

PNB *p*-nitrobenzyl or *p*-nitrobenzoate

pNBZ p-nitrobenzoate PNP p-nitrophenyl

PNPE 2-(4-nitrophenyl)ethyl
PNZ p-nitrobenzylcarbonyl
POC propargyloxycarbonyl
POM 4-pentenyloxymethyl
POM pivaloyloxymethyl

POM [(p-phenylphenyl)oxy]methyl POMB 2-(prenyloxy)methylbenzoate

Ppoc 2-triphenylphosphonioisopropoxycarbonyl

Pp 2-phenyl-2-propyl Ppt diphenylthiophosphinyl

Pre prenyl

Preoc prenyloxycarbonyl
Proc or Poc propargyloxycarbonyl
PSB p-siletanylbenzyl
PSE 2-(phenylsulfonyl)ethyl

Psoc (2-phenyl-2-trimethylsilyl)ethoxycarbonyl

Psec 2-(phenylsulfonyl)ethoxycarbonyl

PTE 2-(4-nitrophenyl)thioethyl

PTM phenylthiomethyl

PTMSE (2-phenyl-2-trimethylsilyl)ethyl

Pv pivaloyl

Px or pixyl 9-(9-phenyl)xanthenyl Pyet 1- $(\alpha$ -pyridyl)ethyl

Pyoc 2-(2'- or 4'-pyridyl)ethoxycarbonyl

Qn 2-quinolinylmethyl
Qm 2-quinolinylmethyl
QUI 4-quinolinylmethyl
SATE S-acetylthioethyl

Scm S-carboxymethylsulfenyl

SEE 1-[2-(trimethylsilyl)ethoxy]ethyl
SEM 2-(trimethylsilyl)ethoxymethyl
SES 2-(trimethylsilyl)ethanesulfonyl
SIBA 1,1,4,4-tetraphenyl-1,4-disilanylidene

Sisyl tris(trimethylsilyl)silyl

SMOM (phenyldimethylsilyl)methoxymethyl Snm S-(N'-methyl-N'-phenylcarbamoyl)sulfenyl

SOB 4-trialkylsilyloxybutyrate

STABASE 1,1,4,4-tetramethyldisilylazacyclopentane TAB 2-{[(methyl(tritylthio)amino]methyl}benzoate

PROTECTIVE GROUPS xxv

Tacm trimethylacetamidomethyl

TBDMS or TBS t-butyldimethylsilyl
TBDPS t-butyldiphenylsilyl

Tbf-DMTr 4-(17-tetrabenzo[a,c,g,i]fluorenylmethyl-4',4''-

dimethoxytrityl

Tbfmoc 17-tetrabenzo [a,c,g,i] fluorenylmethoxycarbonyl

TBDPSE *t*-butyldiphenylsilylethyl

TBDS tetra-t-butoxydisiloxane-1,3-diylidene

TBMPS *t*-butylmethoxyphenylsilyl

TBS or TBDMS *t*-butyldimethylsilyl

TBTr 4,4',4"-tris(benzyloxy)triphenylmethyl TCB 2,2,2-trichloro-1,1-dimethylethyl

TcBOC 1,1-dimethyl-2,2,2-trichloroethoxycarbonyl

TCP N-tetrachlorophthalimido
Tcroc 2-(trifluoromethyl)-6-

chromonylmethyleneoxycarbonyl

Tcrom 2-(trifluoromethyl)-6-chromonylmethylene

TDE (2,2,2-trifluoro-1,1-diphenyl)ethyl

TDG thiodiglycoloyl

TDS thexyldimethylsilyl or tris(2,6-diphenylbenzyl)silyl

Teoc 2-(trimethylsilyl)ethoxycarbonyl

TES triethylsilyl

Tf trifluoromethanesulfonyl

TFA trifluoroacetyl

Tfav 4,4,4-trifluoro-3-oxo-1-butenyl

Thexyl 2,3-dimethyl-2-butyl
THF tetrahydrofuranyl
THP tetrahydropyranyl
TIBS triisobutylsilyl

TIPDS 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene)

TIPS triisopropylsilyl TIX trimethylsilylxylyl

TLTr 4,4',4"-tris(levulinoyloxy)triphenylmethyl

Tmb 2,4,6-trimethylbenzyl
Tmob trimethoxybenzyl
TMPM trimethoxyphenylmethyl

TMS trimethylsilyl

Tms (2-methyl-2-trimethylsilyl)ethyl

TMSE or TSE 2-(trimethylsilyl)ethyl

TMSEC 2-(trimethylsilyl)ethoxycarbonyl
TMSP 2-trimethylsilylprop-2-enyl
TMTr tris(p-methoxyphenyl)methyl
TOB 2-{[(tritylthio)oxy]methyl}benzoate

Tos or Ts *p*-toluenesulfonyl

Tom triisopropylsilyloxymethyl

xxvi ABBREVIATIONS

TPS triphenylsilyl

TPTE 2-(4-triphenylmethylthio)ethyl
Tr triphenylmethyl or trityl

TrtF₇ 2,3,4,4',4",5,6-heptafluorotriphenylmethyl

Tritylone 9-(9-phenyl-10-oxo)anthryl Troc 2,2,2-trichloroethoxycarbonyl

Ts or Tos *p*-toluenesulfonyl

Tsc 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl

TSE or TMSE 2-(trimethylsilyl)ethyl
Tse 2-(p-toluenesulfonyl)ethyl
Tsoc triisopropylsiloxycarbonyl
Tsv p-toluenesulfonylvinyl
Voc vinyloxycarbonyl

Xan xanthenyl

Z or Cbz benzyloxycarbonyl

REAGENTS

9-BBN 9-borabicyclo[3.3.1]nonane

bipy 2,2'-bipyridine

BOP Reagent benzotriazol-1-yloxytris(dimethylamino)

phosphonium hexafluorophosphate

BOP-Cl bis(2-oxo-3-oxazolidinyl)phosphinic chloride BroP bromotris(dimethylamino)phosphonium

hexafluorophosphate

Bt benzotriazol-1-yl or 1-benzotriazolyl BTEAC benzyltriethylammonium chloride

CAL Candida antarctica lipase CAN ceric ammonium nitrate

CMPI 2-chloro-1-methylpyridinium iodide

cod cyclooctadiene
cot cyclooctatetraene
CSA camphorsulfonic acid

DABCO 1,4-diazabicyclo[2.2.2]octane
DBN 1,5-diazabicyclo[4.3.0]non-5-ene
DBAD di-t-butyl azodicarboxylate

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC dicyclohexylcarbodiimide

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEAD diethyl azodicarboxylate
DIAD diisopropyl azodicarboxylate
DIBAL-H diisobutylaluminum hydride
DIPEA diisopropylethylamine
DMAC N,N-dimethylacetamide

REAGENTS xxvii

DMAP 4-*N*,*N*-dimethylaminopyridine

DMB 2,4-dimethoxybenzyl
DMDO 2,2-dimethyldioxirane
DME 1,2-dimethoxyethane
DMF N,N-dimethylformamide

DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMS dimethyl sulfide DMSO dimethyl sulfoxide

dppb 1,4-bis(diphenylphosphino)butane dppe 1,2-bis(diphenylphosphino)ethane

DTE dithioerythritol DTT dithiothreitol

EDC or EDCI 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

(or 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide) hydrochloride

EDCI or EDC 1-ethyl-3-(3-(dimethylaminopropyl)carbodiimide

EDTA ethylenediaminetetraacetic acid

HATU N-[(dimethylamino)(3H-1,2,3-triazolo(4,5-b)

pyridin-3-yloxy)methylene]-*N*-

methylmethanaminium hexafluorophosphate, previously known as *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

1,1,1,3,3,3-hexamethyldisilazane

HMPA hexamethylphosphoramide
HMPT hexamethylphosphorous triamide
HOAt 7-aza-1-hydroxybenzotriazole
HOBT 1-hydroxybenzotriazole
Im imidazol-1-yl or 1-imidazolyl

IPA isopropyl alcohol

HMDS

IPCF (=IPCC) isopropenyl chloroformate (isopropenyl

chlorocarbonate)

KHMDS potassium hexamethyldisilazide
LAH lithium aluminum hydride
LDBB lithium 4.4'-di-t-butylbiphenylide

LDBB lithium 4,4'-di-t-butylbiphenylide MAD methylaluminumbis(2,6-di-t-butyl-4-

methylphenoxide

MCPBA *m*-chloroperoxybenzoic acid MoOPH oxodiperoxymolybdenum(pyridine)

hexamethylphosphoramide

ms molecular sieves
MSA methanesulfonic acid
MTB methylthiobenzene
MTBE t-butyl methyl ether
NBS N-bromosuccinimide
Ni(acac)₂ nickel acetylacetonate

xxviii ABBREVIATIONS

NMM *N*-methylmorpholine

NMO *N*-methylmorpholine *N*-oxide

NMP N-methylpyrrolidinone
P polymer support
Pc phthalocyanine

PCC pyridinium chlorochromate

PdCl₂(tpp)₂ dichlorobis[tris(2-methylphenyl)phosphine]

palladium

Pd₂(dba)₃ tris(dibenzylideneacetone)dipalladium

PG protective group

PhI(OH)OTs [hydroxy(tosyloxy)iodo]benzene
PPL porcine pancreatic lipase
PPTS pyridinium *p*-toluenesulfonate
proton sponge 1,8-bis(dimethylamino)naphthalene

Pyr pyridine

Rh₂(pfb)₄ rhodium perfluorobutyrate

ScmCl methoxycarbonylsulfenyl chloride

SMEAH sodium bis(2-methoxyethoxy)aluminum hydride

Su succinimidyl

TAS-F tris(dimethylamino)sulfonium

difluorotrimethylsilicate

TBAF tetrabutylammonium fluoride

TEA triethylamine

TEBA or TEBAC triethylbenzylammonium chloride triethylbenzylammonium chloride

TESH triethylsilane

Tf trifluoromethanesulfonyl
TFA trifluoroacetic acid
TFAA trifluoroacetic anhydride
TFMSA or TfOH trifluoromethanesulfonic acid
TfOH or TFMSA trifluoromethanesulfonic acid

THF tetrahydrofuran THP tetrahydropyran

TMEDA N,N,N'',N''-tetramethylethylenediamine

TMOF trimethyl orthoformate

TPAP tetrapropylammonium perruthenate

TPP tetraphenylporphyrin

TPPTS sulfonated triphenylphosphine
TPS triisopropylbenzensulfonyl chloride
Tr⁺BF₄ or triphenylcarbenium tetrafluoroborate

Ph₃C⁺BF₄⁻

TrS⁻Bu₄N⁺ tetrabutylammonium triphenylmethanethiolate

Ts toluenesulfonyl